REMARKS

Claims 1, 9-21, 23, 30-32, 38, 41-43, 81-90 and 104-109 were pending in the instant application. Applicants have cancelled claim 31 without prejudice and reserve the right to pursue the subject matter of the cancelled claim in one or more related applications. Applicants have amended claims 1, 12, 23, 32, 42, 81-90 and 106 and have added new claim 110 for clarity to more particularly point out and distinctly claim that which Applicants regard as the invention. Applicants have also amended claims 41 and 42 such that they are now independent and include all limitations of claim 38 from which they previously depended. Applicants have additionally amended withdrawn claims 37, 51, 65, 73, 77, 80, 93, 94, 96, 98 and 100, which are drawn to species of the instant invention and/or a process of use of the instant invention that were not elected in the Restriction Requirement of November 30, 2005, to include all limitations of a claim of the currently pending invention. Support for the amendments and new claim is found throughout the specification; for example, support for the amendments to the withdrawn claims may be found at page 12, lines 15-17, at page 20, lines 16-20, at page 29, lines 7-8, at page 60, lines 6-15 and at page 135, lines 12-21; support for the amendments to claims 1, 23, 42 and 81-90 may be found at page 21, lines 4-8, at page 34, lines 15-16, at page 60, lines 6-15 and at page 135, lines 12-21; support for the amendment to claim 106 may be found at page 36, lines 30-31; support for new claim 110 may be found in Section 5.3.2, beginning at page 88 and at page 133, lines 20-26. Accordingly, no new matter has been introduced. After entry of this amendment, claims 1, 9-21, 23, 30, 32, 38, 41-43, 81-90 and 104-110 will be pending.

The rejections under 35 U.S.C. § 112, second paragraph, should be withdrawn

The Examiner has rejected claims 12, 31, 41 and 109 under 35 U.S.C. § 112, Second Paragraph, for allegedly failing to particularly point out and distinctly claim the invention.

The Examiner contends that claims 12 and 31 are indefinite in the recitation of "B cell activity" and "immune response," respectively, because it is allegedly unclear as to which activity/response or requisite structural/functional characteristics are intended to be encompassed by the claimed antibody.

Applicants respectfully disagree with the Examiner's contentions for reasons of record. Nevertheless, without agreeing with the Examiner and in order to advance prosecution, Applicants have amended claim 12 to delete the phrase "B cell activity" and have cancelled claim 31, rendering the instant rejections moot with respect to these claims.

With respect to the rejection of claims 41 and 109, Applicants' representative, Dr. Richard Enmon, contacted Examiner Crowder on March 28, 2007 regarding the lack of explanation in the Office Action in connection with the rejection of these claims. Examiner Crowder indicated that inclusion of claims 41 and 109 in the rejection was an editorial mistake and that, provided these claims were not dependent on rejected claims 12 or 31, the instant rejection would not be maintained for claims 41 and 109.

In view of the foregoing, Applicants submit that the instant rejections with respect to claims 12, 31, 41 and 109 have been obviated and/or rendered moot and request that the rejections under 35 U.S.C. § 112, Second Paragraph, be withdrawn.

The rejections under 35 U.S.C. 102(b) should be withdrawn

The Examiner has rejected claims 1, 9-16, 23, 30-32, 81-90, 108 and 109 under 35 U.S.C. § 102(b) as allegedly anticipated by Weinrich et al., 1996, Hybridoma 15:109-116 ("Weinrich") as evidenced by Bolland et al., 1999, Adv. Immunol. 72:149-177 ("Bolland") and Clynes et al., 2000, Nature Med. 6:443-446 ("Clynes").

Preliminarily, Applicants note that Weinrich discloses the use of an antibody only in Western blot, immunoblot or immunoprecipitation procedures (*i.e.*, for detection of denatured proteins) and, therefore, does not disclose an antibody that binds FcγRIIB that is endogenously expressed on the surface of a human cell (*i.e.*, a native protein) as required by independent claims 1, 23 and 81-90 as amended herein. The deficiency of Weinrich is not remedied by Bolland or Clynes. Neither Bolland nor Clynes offers any evidence to the binding activity of the antibodies of Weinrich, much less evidence that the antibodies of Weinrich bind FcγRIIB that is endogenously expressed on the surface of a human cell and comprise a variable domain that immunospecifically binds FcγRIIB with greater affinity than FcγRIIA. Moreover, as discussed in the previous Response and Amendment dated October 10, 2006, additional evidence demonstrates that the antibody of Wienrich cited by the Examiner, II8D2, does not bind to FcγRIIB as endogenously expressed on the surface of a human cell. In particular, Table 1 of Budde et al, 1995. "Specificity of CD32 mAb for FcγRIIa, FcγRIIb1, and FcγRIIb2 expressed in transfected mouse B cells and BHK-21 cells, in Leucocyte Typing V, Whit Cell Differentiation Antigens, Vol. I (eds. Schlossman et al.), 828-832 (previously submitted as **Exhibit B** in the Response dated October 10, 2006 and as reference **C09** in the July 15, 2005 IDS) ("Budde"), shows that II8D2 does not bind Daudi cells (a human B-cell line that endogenously expresses FcγRIIB (*see*, Budde, page 828, column 1)) in a FACS analysis. Accordingly, Weinrich, as evidenced by Bolland and Clynes, does not teach each and every element of independent claims 1, 23 and 81-90. Therefore,

Weinrich cannot anticipate these claims. Because Weinrich does not anticipate any of claims 1, 23 and 89-90, the reference does not anticipate remaining claims 9-16, 30, 32 and 108-110 as dependent thereon.

With respect to the Examiner's instant rejection, the basis of the rejection is that the pending independent claims allegedly read on the antibodies of Weinrich. In particular, the Examiner contends that the instant claims, which require, in part, that the claimed antibody specifically binds FcγRIIB that is *endogenously* expressed on the surface of a human cell, encompass the antibodies of Weinrich, which allegedly bind FcγRIIB that is *recombinantly* expressed on the surface of a cell. This rejection is predicated on the contention that the phrase endogenous expression, when used in the context of protein expression in a cell, encompasses the expression of a recombinant protein. Applicants respectfully disagree for the reasons set forth below.

The Examiner supports her position by referencing a definition of endogenous from Merriam-Webster's Collegiate Dictionary, 10th edition, 1997, and citing MPEP § 2111 for the argument that during patent prosecution, pending claims must be given their "broadest reasonable interpretation consistent with the specification" (see Office Action, page 5). Applicants respectfully submit, however, that such interpretation is not without bound, but is, in fact, the "broadest reasonable construction 'in light of the specification *as it would be interpreted by one of skill in the art*'" (emphasis added). See MPEP § 2111, citing Phillips v. AWH Corp., 415 F.3d 1303, 1316 citing In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364 (Fed.Cir. 2004). This requirement to understand the way in which one of skill in the art would use claim terms has also lead the court to recognize the value of extrinsic evidence, including technical dictionaries (although such evidence is "less significant" than intrinsic evidence (*e.g.*, the specification)). See Phillips at 317-318. However, the court specifically cautions against the indiscriminate reliance on "general use" dictionaries at the risk of over breadth in interpretation. See Phillips at 1321-1322.

Recombinant protein expression is not a newly emerging field, and the literature is rife with teachings of both the recombinant proteins themselves and the methods to effect such expression. Applicants submit that in the field of biotechnology, and, in particular, in studies using/investigating recombinant proteins, the term "endogenous" is consistently used to differentiate those proteins that are naturally expressed by a cell from those that the cell has been manipulated to express using recombinant methods. Consistent with the art accepted usage, the instant specification specifically distinguishes proteins as endogenously or recombinantly expressed (see specification at page 12, lines 15-17), distinguishes recombinant expression from other methods of protein production (*e.g.*, expression by

hybridoma cells) (see specification at page 15, lines 31-33), and distinguishes endogenous proteins from transgenic, *i.e.*, recombinant, proteins (see specification at page 32, lines 21-23). The Examiner's attention is also invited to Exhibit A, attached hereto, which is a copy of page 205 of the Oxford Dictionary of Biochemistry and Molecular Biology (Revised Ed., 1997, Oxford University Press) presenting the definition of "endogenous." As set forth in Exhibit A, endogenous refers to substances, "arising or developing within [a]...cell, and excluding any consequences of externally added agents or materials." Applicants also point out that this definition is not inconsistent with that cited by the Examiner in the Office Action, but only a more specific definition of the term as it is used in the field of biotechnology. It would thus be clear to one of skill in the art that the class of proteins which are endogenously expressed does not encompass those which are recombinantly expressed, because recombinant expression requires the manipulation and addition of external agents to a cell.

As further evidence that Weinrich fails to teach or disclose the antibody of the instant invention, the Examiner's attention is again invited to Tam et al., 2004, Allergy 59:772-780 ("Tam"), previously submitted as Exhibit D in the Response and Amendment dated October 10, 2006 and as reference C58 in the July15 IDS in connection with the prosecution of this application. Tam (working in the same field as Weinrich) evidences that those skilled in the art of B-cell function/activity, at a date significantly later than the publication of Weinrich, failed to recognize the antibodies of Weinrich or, in fact, *any* antibody as exhibiting specificity for FcγRIIB, in particular, exhibiting greater affinity for FcγRIIB than for FcγRIIA (see Tam, page 773, 1st column, lines 43-45 and page 777, 2nd column, lines 1-5).

Accordingly, as understood by one of skill in the art, Weinrich does not disclose an antibody that binds to FcγRIIB that is endogenously expressed on the surface of a human cell as required by independent claims 1, 9, 23, and 81-90 and thus cannot anticipate independent claims 1, 9, 23, and 81-90 or claims 9-16, 30, 32 and 108-110 as dependent thereon.

The Examiner also points out that in both the instant specification and the Koenig declaration submitted in connection with the amendment and response dated October 10, 2006 the binding of the claimed antibody is assessed in cells that recombinately express FcγRIIB. However, Applicants point out that the binding of the claimed antibody to endogenously expressed FcγRIIB has also been demonstrated in the instant specification. In particular, Applicants have assessed the binding of the antibodies of the invention to human B lymphocytes in a FACS based analysis (see, *e.g.*, the specification at page 131, lines 20-26; page 135, lines 12-21 and FIG. 8).

By way of explanation, as taught in the instant specification (see, *e.g.*, Table 1 at page

4) and as was known in the art at the time of filing (see, *e.g.*, Tam at page 773, 1st column, lines 35-36), differing types of FcγRII (*e.g.*, FcγRIIB, FcγRIIA) are usually endogenously co-expressed by the same cell. Absent art-accepted antibodies capable of distinguishing among the various FcγRIIs endogenously expressed on the surface of a cell, such cells are not suitable for studies to determine the specificity and/or affinity of a novel antibody for a specific FcγRII, in particular, to determine the affinity for a particular FcγRII relative to another. Accordingly, studies examining the specificity and/or affinities of novel antibodies for receptors in the FcγRII family use cells recombinantly engineered to express only one type or isoform of FcγRII (see, *e.g.*, Budde et al., 1995, "Specificity of CD32 mAb for FcγRIIa, FcγRIIb1, and FcγRIIb2 expressed in transfected mouse B cells and BHK-21 cells, in Leukocyte Typing V, White Cell Differentiation Antigens, Vol. I, (eds. Schlossman et al.), previously submitted as Exhibit B in the amendment and response dated October 10, 2006 and as reference C09 in the July 15, IDS ("Budde")). However, as demonstrated by Budde, Table 1 at page 829, binding to a recombinant FcγRII expressed by a cell does not guarantee binding to an endogenous FcγRII expressed on the surface of a cell. Accordingly, one of skill in the art would recognize that a therapeutically effective antibody would necessarily bind endogenously expressed receptors on the surface of a human cell as required, in part, by independent claims 1, 9, 23, and 81-90.

In view of the foregoing, Applicants request that the rejections under 25 U.S.C. 102(b) be withdrawn.

The rejections under 35 U.S.C. § 103(a) should be withdrawn

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 9 F.3d 1351, 1533, 28 U.S.P.D.Q.2d 1955,1956 (Fed. Cir. 1993). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir.1999), abrogated on other grounds, citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). In particular, the Examiner cannot use

hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Care must be taken to avoid hindsight reconstruction by using Applicants' disclosure "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result" of the claims in question. *Grain Processing Corporation v. American Maize-Products Company*, 840 F.2d 902, 907 (Fed.Cir.1988), citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed.Cir.1983).

Applicants submit that, the Examiner, in raising the obviousness rejections, is employing, perhaps unconsciously, a hindsight reconstruction without casting her mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction does not meet the legal standard for obviousness. Each of the combinations cited by the Examiner is discussed in turn below to demonstrate that, standing in the shoes of the Applicants at the time the present application was filed, there was no suggestion of the invention or reasonable expectation of success in the art.

The Rejection over Reff in view of Ott and Weinrich

The Examiner has rejected claims 1 and 17-21 under 35 U.S.C. § 103(a) as allegedly unpatentable over Reff et al., 2001, Crit. Rev. Oncol. Hematol. 40:25-35 ("Reff") in view of Ott et al., 2001, J. Allergy Clin. Imunol. 108:S95-S98 ("Ott") and Weinrich. Applicants do not agree with the Examiner's contentions for reasons of record.

Applicants do not dispute that the advantages of the humanization of therapeutic antibodies (*i.e.*, the teachings of Reff) had been known or that FcγRIIB as a potential therapeutic target (*i.e.*, the teachings of Ott) had been recognized prior to the instant application. However, Applicants respectfully disagree with the Examiner's contention that Weinrich discloses an antibody comprising a variable domain that binds to the extracellular domain of FcγRIIB that is endogenously expressed on the surface of a human cell with greater affinity than to FcγRIIA. For reasons discussed above, and for reasons of record, Weinrich fails to disclose such an antibody. Without such disclosure, the Examiner fails to establish a *prima facie* case of obviousness. At most, the combination of Reff in view of Ott and Weinrich suggest only that the instantly claimed invention was "obvious to try," which is not the standard for obviousness under 35 U.S.C. § 103. See *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Applicants submit that, prior to the filing of the instant application, neither Ott nor Weinrich , alone or in combination with Reff provide a suggestion or reasonable expectation of success for producing the claimed antibody.

The Rejection over Presta in view of Ott and Weinrich

The Examiner has rejected claims 1 and 104-107 under 35 U.S.C. § 103(a) as unpatentable over Presta, U.S. Patent 6,737,056 ("Presta") in view of Ott and Weinrich. Applicants respectfully disagree for reasons of record.

Presta is directed to the modification of the Fc region of an antibody to alter binding of the Fc region to an FcγR, which Applicants do not dispute was known prior to the filing of the instant application. Therefore, similar to the rejection over Reff in view of Ott and Weinrich, the instant rejection is premised on the disclosure by Weinrich of an antibody that immunospecifically binds the extracellular domain of FcγRIIB that is endogenously expressed on the surface of a human cell with greater affinity than FcγRIIA. As discussed above, Applicants submit that Weinrich has not disclosed or rendered obvious such an antibody and that, absent such disclosure, the Examiner fails to establish a *prima facie* case of obviousness. The disclosure of Presta does not in any manner address the binding of an antibody via its *variable* domain to an antibody-receptor and, therefore, in no way remedies the deficiencies of Weinrich. Accordingly, prior to the filing of the instant application, neither Ott nor Weinrich , alone or in combination with Presta provide a suggestion or reasonable expectation of success for producing the instantly claimed antibody.

Therefore, Applicants respectfully point out that, only with hindsight based upon the inventors' own work and disclosure, does one arrive at the claimed invention and, thus, submit that no *prima facie* case of obviousness is established by the combination of either (i) Reff, Ott and Weinrich or (ii) Presta, Ott and Weinrich.

In view of the foregoing, Applicants request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

Provisional Rejection For Obviousness-Type Double Patenting

Claims 1, 9-21, 23, 30-32, 38, 41-43, 81-90, and 104-109 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 16-20 of U.S. Patent Application Serial No. 11/305,787 ("the '787 application"). The Examiner contends that the claims are not patentably distinct from each other because claims 1-13 and 16-20 of the '787 application are drawn to the same or nearly the same anti FcγRIIB antibody that specifically binds the extracellular domain of human FcγRIIB and/or to an anti-FcγRIIB antibody with Fc modification.

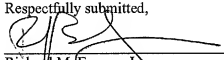
In response, and without agreeing with the rejection, Applicants request that the obvious-type double patenting rejection be held in abeyance until indication of allowable subject matter.

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: April 25, 2007



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